

REMARKS

I. Status of the Claims

Claims 1-6, 29-76 were pending. Claims 1-5, 29 and 58 were examined. Claims 6, 30-57 and 59-76 were withdrawn. The present amendment amends claims 1-5, 29, 30, 32, 33, 35, 37, 38, 40-46 and 48-55, cancels claim 6, 31, 57 and 60-76 and adds new claims 77-94. With the entry of these amendments, claims 1-5, 29, 30, 32-56, 58, 59 and 77-94 are pending.

Applicants note that although claim 59 was withdrawn from consideration, claim 59 falls squarely within the definition of the elected invention (i.e. as being directed to compositions of the compounds of subset (I) of claim 1) and should have been examined with the elected invention.

Claims 1-5, 29, 58, 59 and 77-94 are believed to be readable on the elected invention. Claims 30, 32-56 are readable on methods of use of the claimed invention.

II. Amendments

Claim 1 is amended to be directed to a pharmaceutical composition of compounds as defined in subset (I) of original claim 1, wherein the composition is suitable for human therapeutic administration. Non-elected alternatives are cancelled from the compound definition, and the claim is reworded to further improve its clarity.

Claim 2 is amended to conform to the amendments made to claim 1.

Claims 3-5 and 29 are amended to conform to the amendments made to claim 1, and to insert definitions of the claimed compounds. Non-elected alternatives and certain other compounds are deleted.

Claims 30, 32, 33, 35, 37, 38, 40-46 and 48-55 have been amended to conform to the amendments made to claim 1 (i.e. to recite administering a *composition* as defined in claim 1).

Claims 77-79 have been added and recite compounds within the scope formerly defined in subset (I) of original claim 1.

Claims 80-94 have been added and recite an oral dosage form comprising a composition of the compounds defined in subset (I) of original claim 1.

Former claims 6, 31, 57 and 60-76 have been cancelled.

Applicants wish to emphasize that any subject matter cancelled from the claims by virtue of the present amendments is not abandoned, and Applicants preserve the right to re-present such subject matter by further amendment to the present application or in one or more continuing applications.

III. Request for an Interview

Applicants have carefully considered and addressed the remarks made in the Office Action and believe that they have provided below a complete response addressing the Examiner's remarks. If, however, the response is not deemed to place the application in condition for allowance, issues remain, or new issues have arisen, Applicants request the courtesy of an interview with the Examiner to discuss how prosecution of the application can be brought to a successful conclusion.

IV. Response to the Office Action

A. Incomplete Office Action

Applicants note that claim 59, although dependent from claim 1 and readable on compositions comprising such a compound according to claim 1, was withdrawn from consideration. Applicants believe that the withdrawal of claim 59 was improper and appears to have been in error. Applicants note that Group I as defined in the Office Action August 5, 2010 was defined as encompassing all compounds of claim 1 subset (I) and *compositions comprising the same*. Thus, claim 59 should have been examined with Group I. Restriction between claim 59 and (for example) claim 58 is improper because claims 58 and 59 overlap in scope.

Applicants note that although claim 59 is not included in the claim listing provided by the Examiner for Group I, it was also not listed in any other Group.

B. Claim Objections

Claims 1-5, 29 and 58 were objected to as allegedly containing non-elected subject matter. This objection is believed to be moot in view of the amendment limiting the claims to the compounds of claim 1 subset (I) as specified in the definition of Group I as set forth in the restriction requirement.

C. Rejection of Claims 3-5 and 29 Under 35 U.S.C. 112, Second Paragraph

Claims 3-5 and 29 were rejected as under 35 U.S.C. 112, second paragraph as being allegedly indefinite.

The rejection is moot in view of the amendments. The Office Action alleged that the claims were indefinite because they defined the compound of claim 1 by stating that the structure is defined in "any of Examples 1-6" of the specification, or is one of various compound numbers of the specification. Applicants respectfully disagree that the claims were indefinite because the law is clear that claims must be read in light of the specification, and the specification clearly defined the compounds referred to in claims 3-5 and 29. However, to expedite prosecution of the application, Applicants have inserted definitions of the compounds into the claims.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

D. Rejection of Claims 1 and 58 Under 35 U.S.C. § 102(b)

Claims 1 and 58 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Marumoto *et al.*, *Chem. Pharm. Bull*, 1975, 23(4), 759-774 ("Marumoto").

The Office Action alleged that Marumoto disclosed compounds anticipating claim 1. In particular, the Office Action alleged that:

Marumoto discloses compounds anticipating those instantly elected wherein the compounds comprise the instant variables claims: $X=OH$; $R_2=NH_2$; $R_5=CH_2OH$; $R_6=H$; and, R_1 is C5-alkoxy (see compound 5d), or R_1 is $-OCH_2CH_2OH$ (see compound 51), or R_1 is phenoxy (see compound 5o), or R_1 is substituted phenoxy (see compound 5p or 5q which are substituted with methyl or methoxy in the 3- or 4-positions respectively). The compounds are also used in compositions (see coronary dilator potency). As such, since a species anticipates a genus, and various species are exemplified in the document, claims 1 and 58 are seen to be anticipated.

Office Action p. 3.

Applicants respectfully point out that "[a] claim is anticipated *only if each and every element* as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)) (emphasis added). A rejection for anticipation based on inherency, however, also requires "evidence [that] must make clear that the

missing descriptive matter is *necessarily present* in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). "Inherency, however, *may not be established by probabilities or possibilities*. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Id.* at 1269 (citing *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (quoting *Hansgirk v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939)) (emphasis added)).

Claim 1 has been amended to recite a pharmaceutical composition comprising the compound of formula I and a physiologically acceptable carrier, excipient or diluent, wherein the pharmaceutical composition is suitable for human therapeutic administration.

Applicants respectfully submit that claim 1 as amended clearly distinguishes Marumoto. There does not appear to be any reference to compositions in any of the references to "coronary dilator potency" in Marumoto et al. The end of the first paragraph after the abstract on page 759 states that "we have synthesized new 2-substituted adenosines and assessed their coronary dilator potency.⁷". Footnote 7 refers to "K. Kawazoe and K. Kikuchi, unpublished data" regarding which Marumoto states that "[e]ach of the test compounds was administered *directly* into the coronary artery of anaesthetized, open-chest dog through the polyethylene catheter at doses of 0.1-100µg/dog. The potency of each compound was expressed with the potency of adenosine being taken as unity" (emphasis added). There appears to be no reference elsewhere in Marumoto to the disclosed compounds being part of a pharmaceutical composition. Further, if the compounds of Marumoto were administered to dogs in the manner directly into the coronary artery of a dog, the compounds so administered would not necessarily be in a composition that would be suitable for human therapeutic administration. Accordingly, claim 1 as presently amended is clearly not anticipated by Marumoto.

With respect to claim 58, Applicants respectfully point out that in order for anticipation to be established, it must be shown that each and every element of the claim is necessarily present in the reference. The Office Action, however, did not address how Marumoto allegedly necessarily disclosed a pharmaceutical composition *in unit dose form* and *comprising up to 500mg* of the compound. Further, since claim 58 depends from claim 1, claim 58 is not anticipated for the same reasons as set forth above.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

D. Rejection of Claims 1-5, 29 and 58 Under 35 U.S.C. § 103(a)

Claims 1-5, 29 and 58 were rejected as under 35 U.S.C. § 103(a) as being allegedly obvious over Marumoto. Reconsideration of the rejection is respectfully requested.

The Office Action alleges that Marumoto disclosed compounds and compositions overlapping in scope with the presently claimed compounds. The Office Action concedes that compounds as claimed in claims 2-4 and 29 of the present application were not disclosed by Marumoto. However, the Office Action alleges that many of the compounds listed in claims 2-5 and 29 would have been obvious variants of the species set forth in Marumoto. In particular, the Office alleges that compounds in which R¹ is phenoxy substituted with 4-methyl or 2-methyl would be positional isomers of compound 5p of Marumoto which comprises phenoxy substituted with methyl in the 3-position. The Office alleges that compounds which differ only in the placement of substituents in a ring system are not patentable absent unexpected results.

Applicants respectfully disagree with this ground of rejection. In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) the court held that when a case of *prima facie* obviousness is made based on structural similarity to a known compound, it must be shown that it would have been obvious for the person skilled in the art first to select the particular compound as a lead for modification and then to make the particular modifications to the known compound so as to provide a compound within the scope of the claims. In particular, the court noted that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." The court explained that the defendant's argument that the claimed compounds would have been obvious over a particular prior art compound ("compound b") "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound." In the *Takeda* case, however, the court affirmed a finding that "compound b" would not have been an obvious starting point for modification to discover further compounds because "compound b" exhibited adverse side effects and that "researchers would have been dissuaded from selecting a lead

compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 1358.

For similar reasons to those found in *Takeda*, the person skilled in the art would not have had any reason to regard Marumoto as a starting point for developing new drug compounds for human therapeutic use, and therefore proceed to prepare pharmaceutical compositions of such compounds or to make analogs of such compounds as of the priority date of the present application. This is because it was well known common knowledge in the art at the priority date of the present application that adenosine receptor agonists were not therapeutically useful in humans because of the intolerable side effects that were known to be associated with administration of these compounds. This is explained, for example, in the present application at pp. 1-2 (and the references cited therein), where it is stated that:

"administration of adenosine receptor agonists causes adverse side effects. This has generally precluded the development of adenosine-based therapies. Selective A1 receptor agonists cause bradycardia [reduced heart rate]. A2A receptor agonists cause widespread vasodilation with consequent hypotension and tachycardia. The first selective A2A receptor agonist (2-[4-(2-carboxyethyl)phenylethylamino]-5'-N-ethylcarboxamidoadenosine, or CGS21680), was tested in a Phase 2A clinical trial as a potential anti-hypertensive. However, administration of this compound caused a large fall in blood pressure and consequent increase in cardiac output. This has prevented use of CGS21680 as a medicament. Webb et al. (J. Pharmacol Exp Ther (1991) 259, 1203-1212), Casati et al. (J Pharmacol Exp Ther (1995) 275(2):914-919), and Bonnizone et al. (Hypertension. (1995) 25, 564-9) show that selective A2A adenosine receptor agonists cause hypotension and tachycardia. The degree of tachycardia induced is sufficient to preclude their use as medicaments. Alberti et al. (J Cardiovasc Pharmacol. 1997 Sep;30(3):320-4) discloses that selective A2A adenosine receptor agonists are potent vasodilators that reduce blood pressure and induce marked increments in heart rate and plasma renin activity. These side effects preclude their use as medicaments".

This is also supported by the following documents:

(a) Ribeiro et al., "Adenosine receptors in the nervous system: pathophysiological implications", *Progress in Neurobiology*, 2003, 68, 377-392 (of record)

It is stated in the conclusion of this document that:

However, as noted a long time ago, activation of adenosine receptors at the periphery is associated with hypotension, bradycardia, and hypothermia...

These side effects have so far significantly limited the clinical usefulness of adenosine receptor agonists

Id. (emphasis added).

(b) Oei et al., "Correlation between binding affinities for brain A1 and A2 receptors of adenosine agonists and antagonists and their effects on heart rate and coronary vascular tone." *Journal of Pharmacol. Exp. Ther.*, 1988, 247(3), 882-888 (copy being submitted herewith).

This document reports on the correlation between binding affinities for brain A1 and A2 receptors of adenosine agonists and antagonists and their effects on heart rate and coronary vascular tone. It is stated in the introduction at page 882, in the paragraph bridging the left and right columns, that:

"Many adenosine analogs which display preferential affinity for A1 receptors produce depressions in heart rate, myocardial contractility and impulse conduction velocity ..., whereas those analogs exhibiting greater affinity for A2 receptors produce vasodilation"

Figure 1 of this document shows the concentration-response curves of adenosine agonists on heart rate (top) and coronary flow (bottom) obtained in perfused working rat heart preparations.

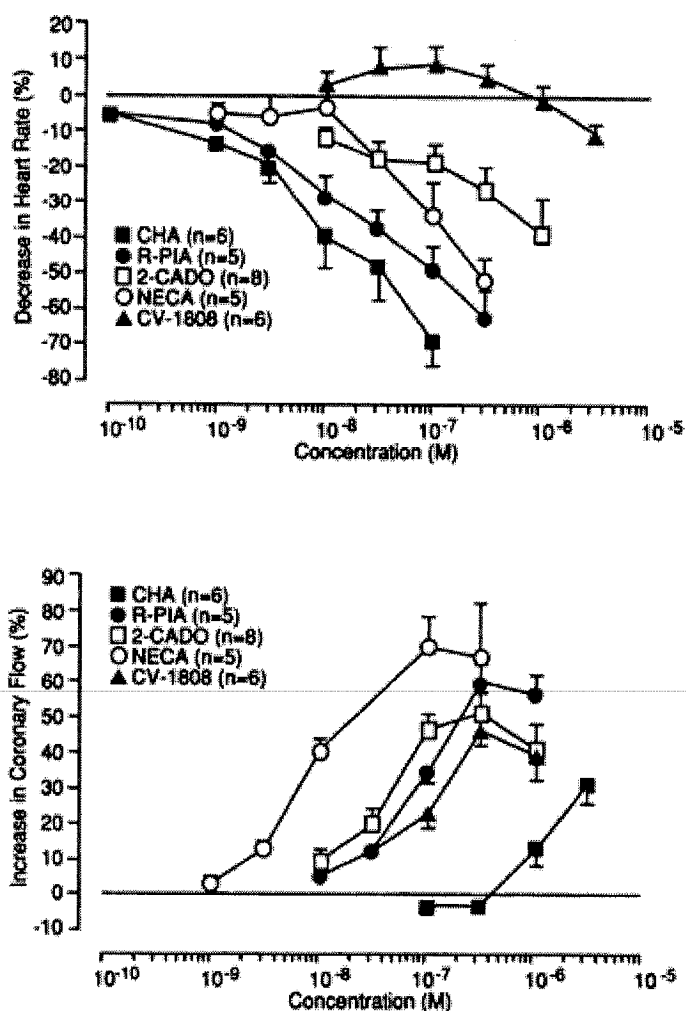


Fig. 1. Concentration-response curves of adenosine agonists on heart rate (top) and coronary flow (bottom) obtained in perfused working rat heart preparations in which perfusion pressure (12 cm H₂O) and aortic pressure (100 cm H₂O) were maintained constant. Hearts were subsequently perfused with the compounds at increasing concentrations. Coronary flow measurements were made at the end of the first half of each 10-min perfusion while the hearts were paced electrically (270 beats/min). Intrinsic heart rates were monitored at the end of the second half of each perfusion period while the electrical pacemaker was stopped. Change in heart rate and coronary flow were expressed in percentage of their corresponding control values. In this group of experiments, the mean control intrinsic heart rate was 224 ± 5 beats/min; mean control coronary flow was 13.1 ± 0.7 ml/min/g wet weight.

As is shown above, all of the selected agonists produced a concentration-dependent effect on heart rate and coronary flow.

(c) Bartlett et al., "Synthesis and Pharmacological Evaluation of a Series of Analogues of 1-Methylisoguanosine", *J. Med. Chem.*, 1981, 24, 947-954 (of record).

This document describes the synthesis and pharmacological evaluation of a series of analogues of 1-Methylisoguanosine, including 2-methoxyadenosine (compound 18). This compound produced hypothermia in mice, and a fall in mean blood pressure (by a striking 41%) and heart rate (by 25%) when administered to rats at 20mg/kg (see Table 1, page 949). The effects on mean blood pressure and heart rate are stated by the authors to be dose-dependent (Abstract, lines 10-12). Such side effects would be intolerable in humans, and so would preclude use of this compound in humans. It is also stated in Bartlett et al (page 950, right column, lines 6-12) that:

The muscle relaxant, hypothermic, and hypotensive effects of the marine natural product 1-methylisoguanosine, as well as a number of the analogues, were accompanied by a decrease in heart rate. *None of the analogues investigated had any selectivity of action whereby the bradycardia could be removed or reduced while maintaining the other pharmacological effects.*

Id. (emphasis added).

Thus, the teaching of Bartlett et al was that the intolerable side effects of 2-methoxyadenosine, and the other compounds investigated, could not be separated from their potential therapeutic effects.

(d) Sawynok et al., "Adenosine Receptor Activation and Nociception", *Eur. J. Pharmacol.* 1998, Vol.347, pp. 1-11. (of record)

This document is a review article on adenosine receptor activation and nociception. It teaches that in the periphery, adenosine A₂ receptor activation produces *pain enhancement* (page 7, left column, section 5, lines 5-7).

Thus, the general teaching in the art at the priority date of the present invention was that the side effects of adenosine receptor agonists could not be separated from their potential therapeutic effects, and so the person of ordinary skill in the art would not have sought to use adenosine receptor agonists as medicaments. The knowledge in the art that adenosine receptor agonists were not therapeutically useful was reinforced by the fact that adenosine receptor agonists have been studied for over 25 years, without any successful therapeutic having being developed.

The present application, however, stems from the Applicants' very surprising discovery that certain adenosine receptor agonists that can be therapeutically effective without causing serious side effects and that they have activity at much lower doses than would be expected to be required to have an effect based on their affinity to adenosine receptors. This is explained in the present application at page 5, second and third paragraphs:

It has surprisingly been found that spongosine is an effective analgesic at doses as much as one hundred times lower than would be expected to be required to have an analgesic effect based on the known affinity of this compound for adenosine receptors. At these doses, spongosine does not cause the significant side effects associated with higher doses of this compound, or other adenosine receptor agonists. Thus, the therapeutic effects of spongosine can be separated from its side effects. The activity of spongosine as an analgesic is the subject of International patent application no. PCT/GB03/05379, and the activity of compounds related to spongosine as analgesics is the subject of International patent application no. PCT/GB04/00935. Use of spongosine and related compounds to treat inflammation and other disorders is the subject of International patent application no. PCT/GB04/000952.

The Applicant has found that spongosine, and the related compounds described in PCT/GB04/00935 and PCT/GB04/000952, have increased affinity for adenosine receptors at pH below pH 7.4. It is believed that this property explains the surprising activity of these compounds at low doses.

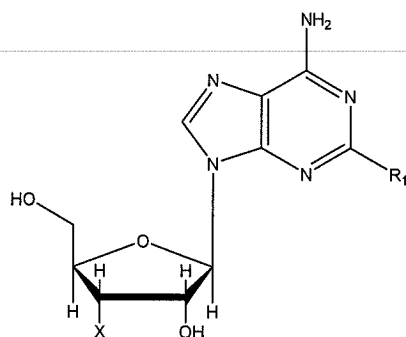
Explanation of why it is believed that this increased affinity at reduced pH means that compounds with this property can be administered without causing serious side effects is given at page 11, second and third paragraphs, of the application:

Compounds of the invention are all believed to have increased affinity for adenosine receptors at pH below pH 7.4. In normal mammalian tissues extracellular pH is tightly regulated between pH 7.35 and 7.45. Some tissues experience lower pH values, particularly the lumen of the stomach (pH between 2 and 3) and the surfaces of some epithelia (for example, the lung surface pH is approximately 6.8). In pathological tissues, for example during inflammation, ischaemia and other types of damage, a reduction in pH occurs.

Because of the increased affinity of compounds of the invention for adenosine receptors at reduced pH, it is thought that the actions of these compounds can be targeted to regions of low pH, such as pathological tissues. Consequently, the doses of these compounds that are required to give therapeutic effects are much lower than would be expected based on their affinity for adenosine receptors at normal extracellular physiological pH. Since only low doses of the compounds are required, the serious side effects associated with administration of adenosine receptor agonists are avoided or minimised. This has

the surprising consequence (contrary to the teaching in the art, for example in US 5,877,180) that some adenosine receptor agonists that are low affinity and/or non-selective agonists at physiological pH (such as spongosine) can be therapeutically effective without causing serious side effects.

The Applicants have found, however, that compounds defined in the claims generally share the property of spongosine of having increased affinity for adenosine receptors at a pH below pH 7.4, even though structurally closely related compounds may not retain this desired activity. In spite of the unpredictability in identifying further substituted adenosines that can be administered with side effects separated from their therapeutic effects, the Applicants have identified certain compounds, recited in the present claims, that have increased affinity for adenosine receptors at reduced pH. Evidence for this is presented in Example 1 of the application, which shows the K_i (nM) values at rat adenosine A2a receptors at pH 5.5 and 7.4 for the compounds defined in the claims.



Compound No.	X	Structure R ₁	(K _i) nM (pH 5.5)	(K _i) nM (pH 7.4)
1	OH	OCH ₃	1.5	1300
2	OH	OCH ₂ CHF ₂	17	780
3	OH	OCH ₂ Cyclopropyl	39	670
4	OH	OCH ₂ CH ₂ CH ₂ CH ₃	11	280
5	OH	O CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	3	1500
6	OH	OPh	71	2500
7	OH	O-(4-cyano)Ph	4	1300
8	OH	O-(3-Ph)Ph	0.7	620
9	OH	O-(2,5-F ₂)Ph	16	2500
10	OH	O-(2,4-F ₂)Ph	16	6400
11	OH	O-(3,4-F ₂)Ph	63	3300
12	OH	O-(2,3,5-F ₃)Ph	46	5900
13	OH	O-(3-Me, 4-F)Ph	43	3100
14	OH	O-(2-Me)Ph	24	22000

Compound No.	X	Structure R ₁	(K _i) nM (pH 5.5)	(K _i) nM (pH 7.4)
15	OH	O-(3-Br)Ph	35	590
16	OH	O-(4-Me)Ph	3.4	720
17	OH	5-indanyloxy	12	760
18	OH	O-(3-CH(CH ₃) ₂)Ph	16	560
19	OH	NHCH ₃	24	1356
20	OH	NHCH ₂ CH ₃	130	1200
21	OH	N(CH ₃) ₂	24	13350
22	OH	NH-(R)-sec-Butyl	33	510
23	OH	NH-(S)-sec-Butyl	29	1400
24	OH	NHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	0.7	290
25	OH	NH-exo-norbornane	5.5	120
26	OH	NHPh	5	160
27	OH	NH-(4-MeO)Ph	3	55
28	OH	NH-(4-F)Ph	10	200
29	OH	NH-cyclopentyl	2.0	420
30	OH	NH-cyclohexyl	0.4	1000
31	OH	N-CH ₃ , N-CH ₂ CH ₂ CH(CH ₃) ₂	26	4000
32	OH	OCH ₂ cyclopentyl	0.2	200
33	OH	SO ₂ CH ₂ CH ₃	100	39000
34	OH	OCH ₂ CH ₂ OH	4	203
35	OH	O-(2,2,3,3-tetrafluoro-cycloButyl)	11	220
36	OH	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	15	800
37	OH	3,5-Me ₂ -Phenyl	24	5500
38	OH	CN	25	175
39	OH	CONH ₂	23	610
40	H	O CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	13	2990

The data show that the claimed compounds surprisingly have increased affinity for adenosine A2A receptors at reduced pH.

The data in Examples 7-13 demonstrate that spongiosine, a compound that also has reduced affinity for adenosine receptors at reduced pH, has analgesic and anti-inflammatory activity at concentrations that do not affect blood pressure or heart rate. It is reasonable to conclude, therefore, that the compounds defined in the present claims can also be used as medicaments without causing serious side effects.

Applicants' insight regarding compounds defined in the claims – based on their discovery of the surprising properties of spongiosine – would not, however, have been obvious to the person skilled in the art from the disclosure in Marumoto.

Based on the general appreciation in the art that adenosine receptor agonists were known *not* to be therapeutically useful and associated with unacceptable side effects, the person skilled in the art would have had no reason to investigate and make structural modifications to the compounds disclosed by Marumoto, or to attempt to make pharmaceutical compositions suitable for human therapeutic administration from such compounds, with any reasonable expectation of success. As the evidence cited by the Applicants has shown, adenosine receptor agonists were, in fact, known in the art *not to be therapeutically useful* and associated with undesirable side effects. Due to the known, serious side effects of adenosine agonists, the skilled person would not have thought to use any of the compounds disclosed in Marumoto as medicaments in the absence of evidence that these compounds could be administered without causing serious side effects. Marumoto report the coronary dilator potency of the compounds investigated. Since this activity causes undesirable reduction in blood pressure, the skilled person would not have made pharmaceutical compositions comprising any of the disclosed compounds because they would also be expected to cause serious side effects. The person skilled in the art would have had even less reason to modify the compounds of Marumoto to make similar compounds with similar properties. This is particularly so given that the majority of Marumoto's compounds, including all of those mentioned in the Office Action, (5d, 5l, 5o, 5p and 5q) had efficacy only comparable to or lower than the potency of adenosine itself.

The Applicants, however, have unexpectedly found that the compounds defined in the claims have increased affinity for adenosine receptors at reduced pH, and from this surprising observation has reason to expect that these compounds can be administered at therapeutically effective doses without causing serious side effects, as has been demonstrated for spongosine.

Based on the foregoing, Applicants respectfully submit that the compositions claimed in the claims as presently amended would not have been obvious over Marumoto.

VI. Conclusion

Applicants respectfully assert that the rejections of record have been overcome by way of this response. Allowance of all claims is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative at 302-530-8837 if there are any questions regarding the claimed invention.

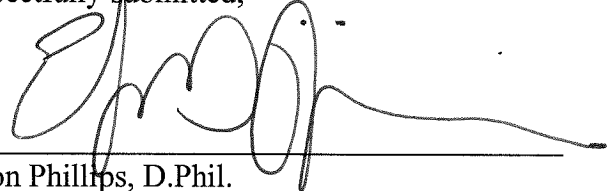
Applicant : Martyn Pritchard et al.
Serial No. : 10/598,520
Filed : December 7, 2007
Page : 36 of 36

Attorney's Docket No.: 13425-0200US1 / BV-1093 US

If not accompanied by an independent petition, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline if necessary. The Commissioner is authorized to debit any fees and apply any credits to Deposit Account No. 06-1050 referencing Attorney Docket No. 13425-0200US1.

Date: May 26, 2011

Respectfully submitted,

A handwritten signature in black ink, appearing to be 'Eifion Phillips', written over a horizontal line.

Eifion Phillips, D.Phil.
Reg. No. 55,538

Customer Number 26161
Fish & Richardson P.C.
Telephone: (302) 652-5070
Facsimile: (877) 769-7945